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Innovations

Solving for X: Accelerators Could Speed Search for Rare Disease Therapies

Wendy Wolfson
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It took 14 years for genetic testing to become accessible enough for Rick and Cristy Spooner of Rancho Santa Margarita, California, to find what was causing Calyn, their oldest daughter, to develop tremors and miss developmental milestones in walking, talking, and comprehension. Their second daughter, Raelyn was born healthy. But their third baby, Ryann, developed the same symptoms as Calyn. The only clue was an anomalous constellation of cells in the two girls' cerebellums seen by MRI. Exome sequencing showed that her daughters had a rare recessive mutation in the NUBPL gene causing a mitochondrial disease called Complex 1 Deficiency. "Our nuclear gene is mutated," Christy Spooner says. "It is very rare." A doctor from the Mayo Clinic told her that it is more common to win the lottery twice than for she and her husband to have that same mutation. Spooner knows of only four other families with the disease.

"The urgency comes from [the knowledge] that 50% of rare disease patients are children and 30% of them will not celebrate their fifth birthday."— Christina Waters, Ph.D.

Could a Rising Tide Lift More Boats?

Christy Spooner's dilemma is common. Only about 400 therapies currently exist for the 7000 estimated rare and neglected diseases. In the US, a disease is considered rare if it affects less than 200,000 people; in Europe, one out of 2000. In aggregate, about 30,000 people in the U.S. and perhaps 300,000 globally are affected by a rare disease.

Books and movies have profiled stories of parents such as John Crowley, now CEO of Amicus Therapeutics, who built Novazyme Pharmaceuticals from a startup to cure his children of Pompe Disease, and the struggle of the Hempel family to get FDA to approve of an experimental therapy for their twins with Niemann-Pick type C1, a neurodegenerative disease. Patient groups are funding research, registries, natural history and biomarker studies and are collaborating with academic researchers and companies on clinical trials to advance therapies. FasterCures, the venture philanthropy advisor started by former financier Michael Milken, now lists 51 consortiums devoted to developing research, therapies, standards, and biomarkers in rare diseases.

According to Cristina Csimma, Ph.D., CEO of Cydan, a new for-profit accelerator for rare diseases located in Cambridge, Massachusetts, four factors are intersecting for the first time: (1) advances in science enabling more precise targeting of disease, (2) the development of sophisticated and influential disease foundations and patient advocacy groups, (3) increased funding due to the influx of the large pharma with substantial external R&D devoted to rare diseases, and (4) a very favorable regulatory environment that provides the opportunities to engage the agencies at a very early stage.

This climate has fostered proliferation of biotechs focusing on rare and ultra rare diseases: Genzyme, Amicus Therapeutics, BioMarin, Ultragenyx, Synageva, and Shire are among the dozens of companies. Due to orphan drug legislation and current reimbursement policies, a company can command a high price for a rare disease drug that fills an unmet need.

A Special Breed of Sheep

Because of the sheer number of diseases and the difficulty of the science involved, even the most established rare disease organizations still struggle for answers. The National Tay-Sachs & Allied Diseases Association (NTSAD) is 56 years old. Children who are born with Tay-Sachs inevitably deteriorate and die, generally before the age of five. Due to carrier screening programs in high-risk populations such as Ashkenazi Jews, the incidence of Tay-Sachs has declined, but anybody can be a carrier, according to Sue Kahn, executive director of the NTSAD. Hence, the Delaware Valley Chapter of the NTSAD is currently conducting studies among Americans of Irish ancestry.

According to Kahn, in the last decade the NTSAD has awarded almost $3 million in research grants and is currently focusing on the Tay-Sachs Gene Therapy Consortium, which is comprised of researchers from Massachusetts General Hospital; the University of Massachusetts Medical Center, Worcester; Auburn University, Boston College; and Cambridge University (U.K.). The Consortium's preclinical work showed encouraging results in animal models, in particular in Jacobs Sheep, a type of heritage sheep, which are natural carriers of Tay-Sachs (the disease also has been found in Muntjak deer, and American flamingos). Funded by a $3.5 million milestone grant from the NIH, the Consortium has collected natural history studies and is refining vectors to get to human trials within a year or two.

"Rare diseases are a not an easy problem to solve," says Kahn.

RARE Science Looks for New Pathways

New rare disease accelerators may help speed the trajectory of certain therapies to patients. "The drug development path traditionally is focused on one drug–one disease," says Christina Waters, Ph.D., founder and CEO of RARE Science, a San Diego-based nonprofit research accelerator of therapies for rare diseases.

"Companies are tackling categories of diseases, and using targeted methods like gene therapy, but there is a need for integrated 'omics' platforms and a change in thinking to focus on the underlying biology of disease to expand use of therapies and make it practical to use drugs across diseases of similar biology." Launched in September 2013, RARE Science is a consortium of researchers from Sanford-Burnham Medical Research Institute; University of California, San Diego; University of California, San Francisco; the Salk Institute; and the Feinberg School of Medicine of Northwestern University. RARE Science board member Dr. David Parkinson is a partner at the venture capital firm New Enterprise Associates (NEA) and CEO of Maryland-based Zyngenia, a preclinical company developing single-molecule biotherapeutics that use multiple pathways simultaneously to treat multifactorial diseases.

The Tay-Sachs genetic mutation results in the insufficient activity of a crucial enzyme, and although there is no cure at this time, in the future this could be addressed with gene therapy. The inadequate enzyme activity also results in many identifiable phenotypes or symptoms such as seizures, which can potentially be treatable with small-molecule therapies. These drugs do not replace the missing enzyme activity in Tay-Sachs, but, according to Waters, developing a better understanding of the molecular pathways involved could support using new combinations of currently approved therapies that could aid in managing the disease phenotypes.

The RARE Science computational platform categorizes diseases according to phenotypes/molecular pathways and can detect shared biology between disparate conditions. It integrates various "omics" methodologies; genomics, transcriptomics, metabolomics, proteomics, and links to mechanisms of approved therapeutics to "reposition" approved drugs. According to Waters, the RARE Science computational platform lends itself to working with rare variants and the mutations driving Mendelian inherited diseases. This involves identifying patient subpopulations, linking their genetic signatures and the resulting biology to a companion therapeutic, and understanding what it takes to get an FDA-approved drug validated and approved for additional disease indications.

"The urgency comes from [the knowledge] that 50% of rare disease patients are children and 30% of them will not celebrate their fifth birthday," says Waters. "They can't wait for a drug discovery program. We really need to find immediate therapeutic solutions in addition to improved diagnostics."

RARE Science collaborates with the Global Genes Project, an Aliso Viejo, California, umbrella patient organization. The next steps are to build networks with childrens' hospitals as well as disease-focused foundations and to get projects commissioned and funded in specific disease areas.

This model is already being used commercially by NuMedii, a Palo Alto, California, based startup cofounded by Stanford professor Dr. Atul Butte and his wife, Dr. Gini Deshpande. Butte, Deshpande, and their colleagues use "Big Data" computing to sift through troves of public data and develop predictive algorithms to detect gene expression profiles in diseases, contrasting and comparing them to those of approved drugs that can activate or block molecular pathways. NuMedii "de-risks" drug candidates and partners with pharma companies for development. The company is funded by Claremont Creek Ventures and Lightspeed Venture Partners.

Cydan Goes Drug Hunting

David Mott, general partner at NEA, recalls a conversation he had at a conference 5 years ago with Dr. Eric Topol, director of the Scripps Translational Science Institute. Topol described how genomics advances were already making it possible to chop up big diseases into smaller ones. What if they could create an accelerator staffed with experienced drug developers who could perform fast validation of projects—or fast kill? Mott launched Cydan in April 2013 with $16 million from NEA, Pfizer Venture Investments, and Alexandria Venture Investments. In October 2013, Lundbeckfond Ventures, and Bay City Capital led an additional $10 million financing round with the prior investors.

"The way science has evolved, we are beginning to understand these diseases at a genetic and molecular level," says Mott. "We are trying to stop disease at its beginning. It is decreasing our expenses in drug development. It is changing its expense-to-risk ratio."

According to Mott, segmenting disease into separate subtypes is already being done in cancer, as with, for example, Crizotinib, an ALK inhibitor for non-small cell lung cancer that the FDA approved in 2011. "Lung cancer is not a single cancer but many different types of cancers that affect the lung," says Mott. "There is a big crossover between rare genetic disease and targeted therapeutics in oncology."

Cydan will screen potential candidates from academic labs and patient foundations in the US and globally. According to Mott, once a compound is selected and passes a 12 month "de-risking" program, the money is already raised and a management team is in place, saving perhaps 6–12 months of downtime that would otherwise be spent in fundraising and setting up a startup infrastructure. The accelerator focuses on the crack between academic research and getting a company staffed and funded. "I think that crack is a very fruitful place to go drug hunting," says Mott.

"Patient foundations are very interested in Cydan's model because we can ask key development questions that can enable rigorous go/no go decisions—and have capital on the table," says Csimma. "They like the fact that we come to the table with a very objective approach because we are not asset centric." Cydan looks for "assets" with well-characterized genetic etiology, usually animal data, or even clinical data in a different indication. Assets would also be backed up by global registries and natural history studies from patient foundations. Assets must provide meaningful clinical benefit for an unmet need and potential for an eventual spinout and/or expanded indications. Successful candidates can then transition smoothly to series A-supported development programs. The accelerator plans to launch up to five companies in 4 years. Cydan will also introduce early stage investors and academics or foundations.

A year after their daughters' diagnosis, the Spooners continue to work with doctors, including Dr. Virginia Kimonis in the

division of Genetics and Metabolism at the University of California, Irvine, to research possible trial drugs. They are considering fundraising to support research opportunities. They are also working with the UMDF (United Mitochondrial Foundation) to stay informed about any drugs or therapies that become available for their disease and/or to treat similar symptoms. "We are not sure if our disease is progressive, so we are very concerned and needing to stay aware and open for treatments and hopefully one day a cure." writes Christy Spooner.

Wendy Wolfson (wendywolfson@nasw.org) is a science writer based in Southern California.